(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 December 2003 (24.12.2003)

PCT

(10) International Publication Number
WO 03/105823 A1

(51) International Patent Classification[7]: A61K 31/202, 31/131, 31/16, 31/22, 31/41, 31/404, 31/381, A61P 43/00

(21) International Application Number: PCT/US03/10817

(22) International Filing Date: 9 April 2003 (09.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/389,035 14 June 2002 (14.06.2002) US

(71) Applicant *(for all designated States except US)*: **ALCON, INC.** [CH/CH]; Bosch 69, P. O. Box 62, CH-6331 Hunenberg (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BARKER, Ronnie, C.** [US/US]; 3608 Lake Pontchartrain Drive, Arlington, TX 76016 (US). **GAMACHE, Daniel, A.** [US/US]; 5610 Hunterwood Lane, Arlington, TX 76017 (US).

(74) Agents: **RYAN, Patrick, M.** et al.; R & D Counsel Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(81) Designated States *(national)*: AU, BR, CA, CN, JP, KR, MX, PL, US, ZA.

(84) Designated States *(regional)*: European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/105823 A1

(54) Title: USE OF HYDROXYEICOSATETRAENOIC ACID COMPOUNDS TO TREAT DRY MOUTH

(57) Abstract: The use of HETE compounds to treat dry mouth is disclosed. According to the methods of the present invention, a HETE compound is administered to the oral cavity of a patient.

Use of Hydroxyeicosatetraenoic Acid Compounds to Treat Dry Mouth

The present invention is directed to the use of hydroxyeicosatetraenoic acid compounds to treat dry mouth.

Background of the Invention

15-Hydroxyeicosatetraenoic acid ("15-HETE") is known to have inhibitory effects on leukotriene B4 production or its activity. See, for example, Zhu, et al., Skin Pharmacology and Applied Skin Physiology, 13(5):235-45 (Sep-Oct 2000); and Heitmann, et al., Experimental Dermatology, 4(2):74-8 (April 1995). 15-HETE is also reported to have minor anti-inflammatory properties in colitis. See Van Dijk, et al., Agents and Actions, 38 Spec. No. C120-1 (1993).

U.S. Patent No. 5,696,166 (Yanni et al.) discloses compositions containing hydroxyeicosatetraenoic acid ("HETE") derivatives and methods of using them topically for treating dry eye. Yanni et al. discovered that compositions comprising HETE derivatives increase ocular mucin secretion and are thus useful in treating dry eye.

It has been reported that 15-HETE can improve psoriasis when injected into psoriatic skin lesions. Fogh, et al., "Improvement of Psoriasis Vulgaris After Intralesional Injections of 15-Hydroxyeicosatetraenoic Acid (15-HETE)." J Am Acad Dermatol, 18:279-85 (1988). At page 284 of this article, Fogh, et al. conclude that, in their experiments, 0.1 ml o f 10 μmol/L (300 ng) of 15-HETE was required to cause a clinical effect.

Millions of people suffer from dry mouth ("xerostomia") due to abnormalities in the secretion of saliva. Dysfunction of salivary glands may be due to autoimmune processes which destroy the salivary glands (e.g., Sjogren's syndrome), radiation therapy for head and neck cancer, and

medications used to treat a variety of conditions. Deprivation of normal saliva may lead to infections, tooth decay and periodontal disease, sores and ulcers. No effective treatment for dry mouth currently exists.

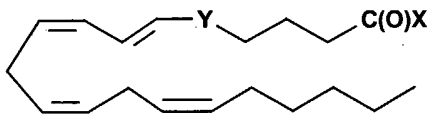
Summary of the Invention

The present invention is directed to methods of using certain HETE compounds to treat dry mouth (known as "xerostomia"). According to the invention, such HETE compounds are administered in an orally acceptable carrier. For example, such HETE compounds could be formulated in a mouth rinse, toothpaste, syrup, chewing gum or in a dissolving tablet. The compositions are administered to the oral cavity of a patient suffering from dry mouth.

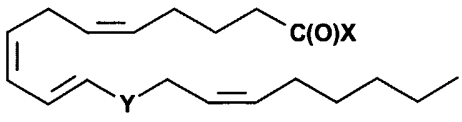
Detailed Description of the Invention

As used herein, "HETE compound" or "HETE compounds" means a compound of formulas **I – XI**.

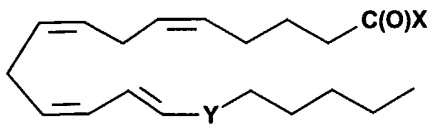
I – III:



(I)



(II); and



(III);

wherein:

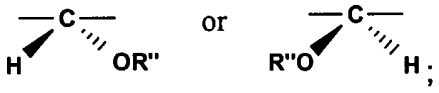
X is $O^- M^+$, OR or NHR';

M^+ is Na^+, K^+, Li^+, Cs^+, and $(A)_4N^+$; and A is independently H, alkyl, cycloalkyl, (cycloalkyl)alkyl, alkyl(cycloalkyl), aryl, arylalkyl, heteroaryl, or $(A)_4N^+$ forms a heteroaryl, heterocycloalkenyl or heterocycloalkyl ring;

R is H, substituted or unsubstituted alkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, arylalkyl, wherein the substitution is made with a moiety selected from the group consisting of: alkyl, halogen, hydroxy and functionally modified hydroxy;

R' is H, substituted or unsubstituted alkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, arylalkyl, wherein the substitution is made with a moiety selected from the group consisting of: alkyl, halogen, hydroxy and functionally modified hydroxy; and

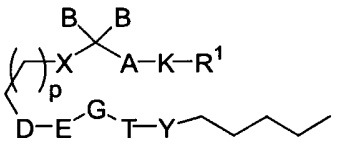
Y is



;

wherein R'' is H or C(O)R;

IV:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2-Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$, or 2,3,4,5-tetrazol-1-yl, wherein:

R is H or CO_2R forms a pharmaceutically acceptable salt or a pharmaceutically acceptable ester;

NR^2R^3 and NR^5R^6 are the same or different and comprise a free or functionally modified amino group, e.g., R^2, R^3, R^5 and R^6 are the same or different and are H, alkyl, cycloalkyl, aralkyl, aryl, OH, or alkoxy, with the proviso that at most only one of R^2 and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 comprises a free or functionally modified hydroxy group, e.g., R^4 is H, acyl; alkyl, cycloalkyl, aralkyl, or aryl;

Hal is F, Cl, Br or I;

SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H, or $COSR^{21}$ forms a pharmaceutically acceptable salt or a pharmaceutically acceptable thioester;

K is C_2-C_8 alkyl, alkenyl, or alkynyl, or a C_3-C_8 allenyl group;

A and X are the same or different and are a direct bond, CH_2, NR^7, O, or S, with the proviso that at least one of A and X is NR^7, O, or S;

B is H, or BB together comprises a double bonded O, S, or NR^8, with the proviso that BB comprises a double bonded O, S, or NR^8 when A and X are the same or different and are NR^7, O, or S; wherein:

NR^7 and NR^8 are the same or different and comprise a functionally modified amino group, e.g., R^7 and R^8 are the same or different and are H, alkyl, cycloalkyl, aryl, aralkyl, acyl, OH, or alkoxy;

p is 0 or 1;

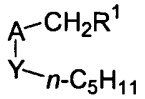
D-E, G-H are the same or different and are CH_2CH_2, CH=CH, or C≡C; and

Y is C(O) (*i.e.* a carbonyl group) or Y is

;

wherein R^9O constitutes a free or functionally modified hydroxy group;

V:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$, or 2,3,4,5-tetrazol-1-yl, where:

R is H or a pharmaceutically acceptable cation, or CO_2R forms a pharmaceutically acceptable ester moiety;

NR^2R^3, NR^5R^6 are the same or different and comprise a free or functionally modified amino group;

OR^4 comprises a free or functionally modified hydroxy group;

Hal is F, Cl, Br, or I;

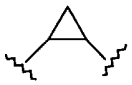
R^{20} is H, alkyl, acyl;

R^{21} is H or a pharmaceutically acceptable cation, or $COSR^{21}$ forms a pharmaceutically acceptable thioester moiety;

A is L_1-A_1-L_2, L_1-A_2-L_2, L_3-A_2-L_4, or L_5-A_2-L_3;

A_1 is CH_2CH_2;

A_2 is



;

L_1 is CH_2-B-D;

B and D are the same or different and are CH_2CH_2, CH=CH, or C≡C;

L_2 is CH_2-K-CH_2CH_2;

K is CH_2CH_2, CH=CH, or C≡C;

L_3 is $CH_2CH_2CH_2$, CH_2CH=CH, CH_2C≡C, CH=$CHCH_2$, C≡CCH_2, or CH=C=CH;

L_4 is X-CH_2CH_2;

X is CH_2CH_2CH=CH, CH_2CH_2C≡C, $CH_2CH_2CH_2CH_2$, CH_2CH=$CHCH_2$, CH_2C≡CCH_2, CH=$CHCH_2CH_2$, C≡CCH_2CH_2, CH_2CH=C=CH, or CH=C=$CHCH_2$;

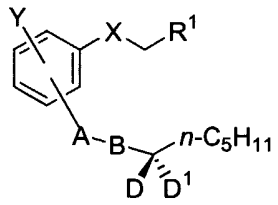
L_5 is CH_2CH_2-B-D; and

Y is C(O) (*i.e.* a carbonyl group) or Y is

;

wherein R^9O constitutes a free or functionally modified hydroxy group;

VI:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$ or 2,3,4,5-tetrazol-1-yl, wherein:

R is H or CO_2R forms a pharmaceutically acceptable salt or a pharmaceutically acceptable ester;

NR^2R^3 and NR^5R^6 are the same or different and comprise a free or functionally modified amino group, e.g., R^2, R^3, R^5 and R^6 are the same or different and are H, alkyl, cycloalkyl, aralkyl, aryl, OH or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 comprises a free or functionally modified hydroxy group, e.g., R^4 is H, acyl; alkyl, cycloalkyl, aralkyl or aryl;

Hal is F, Cl, Br or I;

SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H or $COSR^{21}$ forms a pharmaceutically acceptable salt or a pharmaceutically acceptable thioester;

X is C_2-C_5 alkyl, alkynyl, or alkenyl or a C_3-C_5 allenyl group;

Y is H, free or functionally modified hydroxy group, halo, trihalomethyl, free or functionally modified amino group, free or functionally modified thiol group, $C(O)R^7$, or alkyl;

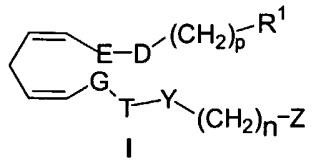
R^7 is H, OH, alkyl, alkoxy, amino, alkylamino or alkoxyamino;

A is a direct bond or C_{1-3} alkyl;

B is CH_2CH_2, *cis*- or *trans*-CH=CH, or C≡C; and

one of D and D^1 is H and the other is a free or functionally modified OH group, or DD^1 together comprises a double bonded oxygen;

VII:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$ or 2,3,4,5-tetrazol-1-yl, wherein:

R is H or CO_2R forms a pharmaceutically acceptable salt or a pharmaceutically acceptable ester;

NR^2R^3 and NR^5R^6 are the same or different and comprise a free or functionally modified amino group, e.g., R^2, R^3, R^5 and R^6 are the same or different and are H, alkyl, cycloalkyl, aralkyl, aryl, OH, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 comprises a free or functionally modified hydroxy group, e.g., R^4 is H, acyl; alkyl, cycloalkyl, aralkyl or aryl;

Hal is F, Cl, Br or I;

SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H or $COSR^{21}$ forms a pharmaceutically acceptable salt or a pharmaceutically acceptable thioester;

E-D is $CH_2CH_2CH_2$ or *cis*-CH_2CH=CH; or E is *trans*-CH=CH and D is CH(OH) in either configuration, wherein the OH is free or functionally modified; or E is CH_2CH_2 and D is a direct bond;

p is 1 or 3 when E-D is $CH_2CH_2CH_2$ or *cis*-CH_2CH=CH, or when E is *trans*-CH=CH and D is CH(OH) in either configuration, wherein the OH is free or functionally modified; or p is 0 when E is CH_2CH_2 and D is a direct bond;

G-T is CH_2CH_2, $CH(SR^7)CH_2$ or *trans*-CH=CH;

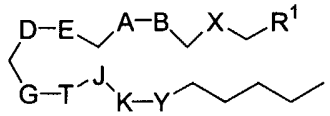
R^7 is H, alkyl, aryl, aralkyl, cycloalkyl or acyl;

Y is CH(OH) in either configuration, in which the OH is free of functionally modified, or C=O (*i.e.*, a carbonyl group);

n is 0, 2 or 4; and

Z is CH_3, CO_2R, $CONR^2R^3$ or CH_2OR^4;

VIII:



I

wherein:

R^1 is $(CH_2)_nCO_2R$, $(CH_2)_nCONR^2R^3$, $(CH_2)_nCH_2OR^4$, $(CH_2)_nCH_2NR^5R^6$, $(CH_2)_nCH_2N_3$, $(CH_2)_nCH_2Hal$, $(CH_2)_nCH_2NO_2$, $(CH_2)_nCH_2SR^{20}$, $(CH_2)_nCOSR^{21}$ or $(CH_2)_n$-2,3,4,5-tetrazol-1-yl, wherein:

R is H or CO_2R forms a pharmaceutically acceptable salt or a pharmaceutically acceptable ester;

NR^2R^3 and NR^5R^6 are the same or different and comprise a free or functionally modified amino group, e.g., R^2, R^3, R^5 and R^6 are the same or different and are H, alkyl, cycloalkyl, aralkyl, aryl, OH, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 comprises a free or functionally modified hydroxy group, e.g., R^4 is H, acyl; alkyl, cycloalkyl, aralkyl, or aryl;

Hal is F, Cl, Br or I;

SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H or $COSR^{21}$ forms a pharmaceutically acceptable salt or a pharmaceutically acceptable thioester;

n is 0 or 2;

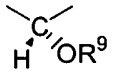
X is O, $S(O)_p$, NR^7 or CH_2, with the proviso that X cannot be CH_2 when n is 0;

p is 0, 1 or 2;

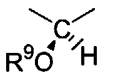
NR^7 comprises a free or functionally modified amino group, e.g., R^7 is H, alkyl, cycloalkyl, aralkyl, aryl, OH or alkoxy,

A-B, D-E, G-T and J-K are the same or different and are CH_2CH_2, CH=CH or C≡C, with the proviso that at least one of A-B, D-E, G-T and J-K must be CH=CH or C≡C; and

Y is C(O) (i.e., a carbonyl), or Y is



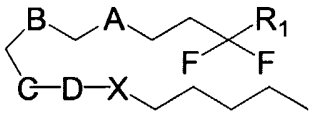
or



;

wherein R^9O constitutes a free or functionally modified hydroxy group;

IX:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$ or 2,3,4,5-tetrazol-1-yl, wherein:

R is H or CO_2R forms a pharmaceutically acceptable salt or a pharmaceutically acceptable ester;

NR^2R^3 and NR^5R^6 are the same or different and comprise a free or functionally modified amino group, e.g., R^2, R^3, R^5 and R^6 are the same or different and are H, alkyl, cycloalkyl, aralkyl, aryl, OH, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 comprises a free or functionally modified hydroxy group, e.g., R^4 is H, acyl; alkyl, cycloalkyl, aralkyl, or aryl;

Hal is F, Cl, Br or I;

SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H or $COSR^{21}$ forms a pharmaceutically acceptable salt or a pharmaceutically acceptable thioester;

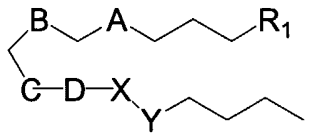
A, B, C and D are the same or different and are C_1-C_5 alkyl, alkenyl, or alkynyl or a C_3-C_5 allenyl group;

X is C(O) (*i.e.* a carbonyl group) or X is

or ;

wherein R^9O constitutes a free or functionally modified hydroxy group;

X:



I

wherein:

R^1 is $(CH_2)_nCO_2R$, $(CH_2)_nCONR^2R^3$, $(CH_2)_nCH_2OR^4$, $(CH_2)_nCH_2NR^5R^6$, $(CH_2)_nCH_2N_3$, $(CH_2)_nCH_2Hal$, $(CH_2)_nCH_2NO_2$, $(CH_2)_nCH_2SR^{20}$, $(CH_2)_nCOSR^{21}$ or $(CH_2)_n$-2,3,4,5-tetrazol-1-yl, wherein:

R is H or CO_2R forms a pharmaceutically acceptable salt or a pharmaceutically acceptable ester;

NR^2R^3 and NR^5R^6 are the same or different and comprise a free or functionally modified amino group, e.g., R^2, R^3, R^5 and R^6 are the same or different and are H, alkyl, cycloalkyl, aralkyl, aryl, OH, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 comprises a free or functionally modified hydroxy group, e.g., R^4 is H, acyl; alkyl, cycloalkyl, aralkyl, or aryl;

Hal is F, Cl, Br or I;

SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H or $COSR^{21}$ forms a pharmaceutically acceptable salt or a pharmaceutically acceptable thioester;

n is 0 or 2;

A, B, C and D is C_1-C_5 alkyl, alkenyl, or alkynyl or a C_3-C_5 allenyl group;

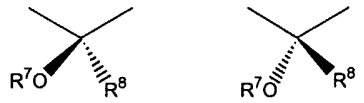
Y is

or ;

wherein R^8 is H or CH_3, and

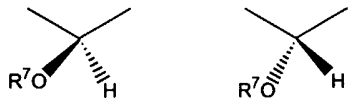
X is CH_2, $CH(CH_3)$ or $C(CH_3)_2$; or

Y is CH_2, $CH(CH_3)$ or $C(CH_3)_2$, and X is



or ;

wherein R^8 is H or CH_3, with the proviso that Y cannot be CH_2 when X is

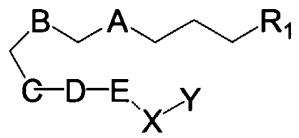


or

; and

R^7O comprises a free or functionally modified hydroxy group; and

XI:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$, or 2,3,4,5-tetrazol-1-yl, where:

R is H or a pharmaceutically acceptable cation, or CO_2R forms a pharmaceutically acceptable ester moiety;

NR^2R^3, NR^5R^6 are the same or different and comprise a free or functionally modified amino group;

OR^4 comprises a free or functionally modified hydroxy group;

Hal is F, Cl, Br, or I;

SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H or a pharmaceutically acceptable cation, or $COSR^{21}$ forms a pharmaceutically acceptable thioester moiety;

A, B, C, D are the same or different and are C_1-C_5 alkyl, C_2-C_5 alkenyl, C_{1-5} cyclopropyl, C_2-C_5 alkynyl, or a C_3-C_5 allenyl group;

E is

;

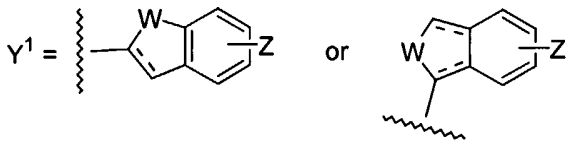
or

where OR^7 comprises a free or functionally modified hydroxy group;

X = $(CH_2)_m$ or $(CH_2)_mO$, where m = 1-6; and

Y = a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, acyl, or a free or functionally modified hydroxy, amino, or thiol group; or

X-Y = $(CH_2)_pY^1$; where p = 0-6; and



wherein:

W = CH_2, O, $S(O)_q$, NR^8, CH_2CH_2, CH=CH, CH_2O, $CH_2S(O)_q$, CH=N, or CH_2NR^8; where q = 0-2, and R^8 = H, alkyl, or acyl;

Z = H, alkyl, acyl, halo, trihalomethyl, or a free or functionally modified amino, thiol, or hydroxy group; and

---- = single or double bond;

or X-Y = cyclohexyl.

Preferred HETE compounds include the compounds of formulas **I – III** wherein X is a pharmaceutically acceptable salt containing a cation selected from the group consisting of: Na^+; K^+; Li^+; Cs^+; and $(A)_4N^+$; and A is independently H, alkyl, cycloalkyl, (cycloalkyl)alkyl, alkyl(cycloalkyl), aryl, arylalkyl, heteroaryl, or $(A)_4N^+$ forms a heteroaryl, heterocycloalkenyl or heterocycloalkyl ring.

Included within the scope of the present invention are the individual enantiomers of the HETE compounds, as well as their racemic and non-racemic mixtures. The individual enantiomers can be enantioselectively synthesized from the appropriate enantiomerically pure or enriched starting material by means such as those described below. Alternatively, they may be enantioselectively synthesized from racemic/non-racemic or achiral starting materials. (*Asymmetric Synthesis*; J. D. Morrison and J. W. Scott, Eds.; Academic Press Publishers: New York, 1983-1985, volumes 1-5; *Principles of Asymmetric Synthesis;* R.E. Gawley and J. Aube, Eds.; Elsevier Publishers: Amsterdam, 1996). They may also be isolated from racemic and non-racemic mixtures by a number of known methods, e.g. by purification of a sample by chiral HPLC (*A Practical Guide to Chiral Separations by HPLC*; G. Subramanian, Ed.; VCH Publishers: New York, 1994; *Chiral Separations by HPLC*; A.M. Krstulovic, Ed.; Ellis Horwood Ltd. Publishers, 1989), or by enantioselective hydrolysis of a carboxylic acid ester sample by an enzyme (Ohno, M.; Otsuka, M. Organic Reactions, volume 37, page 1 (1989)). Those skilled in the art will appreciate that racemic and non-racemic mixtures may be obtained by several means, including without limitation, nonenantioselective synthesis, partial resolution, or even mixing samples having different enantiomeric ratios. Departures may be made from such details within the scope of the accompanying claims without departing from the principles of the invention and without sacrificing its advantages. Also included within the scope of the present invention are the individual isomers substantially free of their respective enantiomers.

The term "free hydroxy group" means an OH. The term "functionally modified hydroxy group" means an OH which has been functionalized to form: an ether, in which an alkyl, aryl, cycloalkyl, heterocycloalkyl, alkenyl, cycloalkenyl, heterocycloalkenyl, alkynyl, or heteroaryl group is substituted for the hydrogen; an ester, in which an acyl group is substituted for the hydrogen; a carbamate, in which an aminocarbonyl group is substituted for the hydrogen; or a carbonate, in which an aryloxy-, heteroaryloxy-, alkoxy-, cycloalkoxy-, heterocycloalkoxy-, alkenyloxy-, cycloalkenyloxy-, heterocycloalkenyloxy-, or alkynyloxy-carbonyl group is substituted for the hydrogen. Preferred moieties include OH, $OCH_2C(O)CH_3$,$OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, and $OC(O)C_2H_5$.

The term "free amino group" means an NH_2. The term "functionally modified amino group" means an NH_2 which has been functionalized to form: an aryloxy-, heteroaryloxy-, alkoxy-, cycloalkoxy-, heterocycloalkoxy-, alkenyl-, cycloalkenyl-, heterocycloalkenyl-, alkynyl-, or hydroxy-amino group, wherein the appropriate group is substituted for one of the hydrogens; an aryl-, heteroaryl-, alkyl-, cycloalkyl-, heterocycloalkyl-, alkenyl-, cycloalkenyl-, heterocycloalkenyl-, or alkynyl-amino group, wherein the appropriate group is substituted for one or both of the hydrogens; an amide, in which an acyl group is substituted for one of the hydrogens; a carbamate, in which an aryloxy-, heteroaryloxy-, alkoxy-, cycloalkoxy-, heterocycloalkoxy-, alkenyl-, cycloalkenyl-, heterocycloalkenyl-, or alkynyl-carbonyl group is substituted for one of the hydrogens; or a urea, in which an aminocarbonyl group is substituted for one of the hydrogens. Combinations of these substitution patterns, for example an NH_2 in which one of the hydrogens is replaced by an alkyl group and the other hydrogen is replaced by an alkoxycarbonyl group, also fall under the definition of a functionally modified amino group and are included within the scope of the present invention. Preferred moieties include NH_2, $NHCH_3$, NHC_2H_5, $N(CH_3)_2$, $NHC(O)CH_3$, NHOH, and $NH(OCH_3)$.

The term "free thiol group" means an SH. The term "functionally modified thiol group" means an SH which has been functionalized to form: a

thioether, where an alkyl, aryl, cycloalkyl, heterocycloalkyl, alkenyl, cycloalkenyl, heterocycloalkenyl, alkynyl, or heteroaryl group is substituted for the hydrogen; or a thioester, in which an acyl group is substituted for the hydrogen. Preferred moieties include SH, $SC(O)CH_3$, SCH_3, SC_2H_5, $SCH_2C(O)C_2H_5$, and $SCH_2C(O)CH_3$.

The term "acyl" represents a group that is linked by a carbon atom that has a double bond to an oxygen atom and a single bond to another carbon atom.

The term "alkyl" includes straight or branched chain aliphatic hydrocarbon groups that are saturated and have 1 to 15 carbon atoms. The alkyl groups may be interrupted by one or more heteroatoms, such as oxygen, nitrogen, or sulfur, and may be substituted with other groups, such as halogen, hydroxyl, aryl, cycloalkyl, aryloxy, or alkoxy. Preferred straight or branched alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and *t*-butyl.

The term "cycloalkyl" includes straight or branched chain, saturated or unsaturated aliphatic hydrocarbon groups which connect to form one or more rings, which can be fused or isolated. The rings may be substituted with other groups, such as halogen, hydroxyl, aryl, aryloxy, alkoxy, or lower alkyl. Preferred cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "$C_1 - C_5$ cyclopropyl" means an alkyl chain of 1 to 5 carbon atoms containing a cyclopropyl group wherein the cyclopropyl group may start, be contained in or terminate the alkyl chain.

The term "heterocycloalkyl" refers to cycloalkyl rings that contain at least one heteroatom such as O, S, or N in the ring, and can be fused or isolated. The rings may be substituted with other groups, such as halogen, hydroxyl, aryl, aryloxy, alkoxy, or lower alkyl. Preferred heterocycloalkyl

groups include pyrrolidinyl, tetrahydrofuranyl, piperazinyl, and tetrahydropyranyl.

The term "alkenyl" includes straight or branched chain hydrocarbon groups having 1 to 15 carbon atoms with at least one carbon-carbon double bond, the chain being optionally interrupted by one or more heteroatoms. The chain hydrogens may be substituted with other groups, such as halogen. Preferred straight or branched alkenyl groups include, allyl, 1-butenyl, 1-methyl-2-propenyl and 4-pentenyl.

The term "cycloalkenyl" includes straight or branched chain, saturated or unsaturated aliphatic hydrocarbon groups which connect to form one or more non-aromatic rings containing a carbon-carbon double bond, which can be fused or isolated. The rings may be substituted with other groups, such as halogen, hydroxyl, alkoxy, or lower alkyl. Preferred cycloalkenyl groups include cyclopentenyl and cyclohexenyl.

The term "heterocycloalkenyl" refers to cycloalkenyl rings which contain one or more heteroatoms such as O, N, or S in the ring, and can be fused or isolated. The rings may be substituted with other groups, such as halogen, hydroxyl, aryl, aryloxy, alkoxy, or lower alkyl. Preferred heterocycloalkenyl groups include pyrrolidinyl, dihydropyranyl, and dihydrofuranyl.

The term "carbonyl group" represents a carbon atom double bonded to an oxygen atom, wherein the carbon atom has two free valencies.

The term "aminocarbonyl" represents a free or functionally modified amino group bonded from its nitrogen atom to the carbon atom of a carbonyl group, the carbonyl group itself being bonded to another atom through its carbon atom.

The term "lower alkyl" represents alkyl groups containing one to six carbons (C_1-C_6).

The term "halogen" represents fluoro, chloro, bromo, or iodo.

The term "aryl" refers to carbon-based rings which are aromatic. The rings may be isolated, such as phenyl, or fused, such as naphthyl. The ring hydrogens may be substituted with other groups, such as lower alkyl, halogen, free or functionalized hydroxy, trihalomethyl, *etc.* Preferred aryl groups include phenyl, 3-(trifluoromethyl)phenyl, 3-chlorophenyl, and 4-fluorophenyl.

The term "heteroaryl" refers to aromatic hydrocarbon rings which contain at least one heteroatom such as O, S, or N in the ring. Heteroaryl rings may be isolated, with 5 to 6 ring atoms, or fused, with 8 to 10 atoms. The heteroaryl ring(s) hydrogens or heteroatoms with open valency may be substituted with other groups, such as lower alkyl or halogen. Examples of heteroaryl groups include imidazole, pyridine, indole, quinoline, furan, thiophene, pyrrole, tetrahydroquinoline, dihydrobenzofuran, and dihydrobenzindole.

The terms "aryloxy", "heteroaryloxy", "alkoxy", "cycloalkoxy", "heterocycloalkoxy", "alkenyloxy", "cycloalkenyloxy", "heterocycloalkenyloxy", and "alkynyloxy" represent an aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, alkenyl, cycloalkenyl, heterocycloalkenyl, or alkynyl group, respectively, attached through an oxygen linkage.

The terms "alkoxycarbonyl", "aryloxycarbonyl", "heteroaryloxycarbonyl", "cycloalkoxycarbonyl", "heterocycloalkoxycarbonyl", "alkenyloxycarbonyl", "cycloalkenyloxycarbonyl", "heterocycloalkenyloxycarbonyl", and "alkynyloxycarbonyl" represent an alkoxy, aryloxy, heteroaryloxy, cycloalkoxy, heterocycloalkoxy, alkenyloxy, cycloalkenyloxy, heterocycloalkenyloxy, or alkynyloxy group, respectively, bonded from its oxygen atom to the carbon of a carbonyl group, the carbonyl group itself being bonded to another atom through its carbon atom.

According to the methods of the present invention a HETE compound of formulas I – **XI** is applied topically to the oral cavity of a person suffering from dry mouth. The compositions used in the methods of the present invention comprise a pharmaceutically effective amount of one or more HETE compounds of formulas **I - XI** and an orally acceptable carrier. Suitable orally acceptable carriers are known in the art and include, but are not limited to, mouth rinses, toothpastes, syrups, chewing gums, and dissolving tablets.

As used herein, the term "pharmaceutically effective amount" refers to an amount of one or more compounds of formulas **I - XI** that, when administered to a patient, reduces or eliminates dry mouth by increasing mucin secretion in the oral cavity. Generally, the compounds of formulas **I - XI** will be contained in a composition of the present invention in a concentration range of about 0.000001 to 10 per cent weight/volume ("% w/v"). Preferably, the compositions will contain one or more compounds of formulas I - XI in a concentration of from about 0.00001-0.01% w/v.

An appropriate buffer system (e.g., sodium phosphate, sodium acetate, sodium citrate, sodium borate or boric acid) may be added to the compositions to prevent pH drift under storage conditions. The particular concentration will vary, depending on the agent employed. In general, however, the buffering agent will be present in an amount sufficient to hold the pH within the range 6.5 – 8.0, preferably 6.8 – 7.6.

Antioxidants may be added to compositions of the present invention to protect the compounds of formulas **I - XI** from oxidation during storage. Examples of such antioxidants include, but are not limited to, vitamin E and analogs thereof, ascorbic acid and derivatives, and butylated hydroxyanisole (BHA).

The following examples are presented to illustrate various aspects of the present invention, but are not intended to limit the scope of the invention in any respect.

Example 1

Ingredient	Amount (% w/v)
Compound of formulas **I - XI**	0.00001-0.01
Ethanol	0.0505
Polyoxyl 40 Stearate	0.1
Boric Acid	0.25
Sodium Chloride	0.75
Disodium Edetate	0.01
Polyquaternium-1	0.001
NaOH/HCl	q.s., pH = 7.5
Purified Water	q.s. 100%

The above composition is prepared by the following method. The batch quantities of polyoxyl 40 stearate, boric acid, sodium chloride, disodium edetate, and polyquaternium-1 are weighed and dissolved by stirring in 90% of the batch quantity of purified water. The pH is adjusted to 7.5 ± 0.1 with NaOH and/or HCl. Under yellow light or reduced lighting, the batch quantity of the compound of formulas **I – XI** as a stock solution in ethanol and the additional quantity of ethanol necessary for the batch are measured and added. Purified water is added to q.s. to 100%. The mixture is stirred for five minutes to homogenize and then filtered through a sterilizing filter membrane into a sterile recipient. Preferably, the above process is performed using glass, plastic or other non-metallic containers or containers lined with such materials.

Example 2

Ingredient	Amount (% w/v)
Compound of formulas **I - XI**	0.00001-0.01
Polyoxyl 40 Stearate	0.1
Boric Acid	0.25
Sodium Chloride	0.75
Disodium Edetate	0.01
Polyquaternium-1	0.001
NaOH/HCl	q.s., pH = 6.5 - 8
Purified Water	q.s. 100%

The above formulation may be made by a method similar to the method described in Example 1.

Example 3

Ingredient	Amount (% w/v)
Compound of formulas **I - XI**	0.00001-0.01
Polyoxyl 40 Stearate	0.1
Ethanol	0.005-0.2
Boric Acid	0.25
Sodium Chloride	0.75
NaOH/HCl	q.s., pH = 6.5 - 8
Purified Water	q.s. 100%

The above formulation may be made by a method similar to the method described in Example 1.

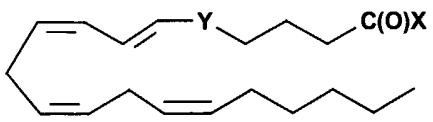
The invention in its broader aspects is not limited to the specific details shown and described above. Departures may be made from such details

within the scope of the accompanying claims without departing from the principles of the invention and without sacrificing its advantages.

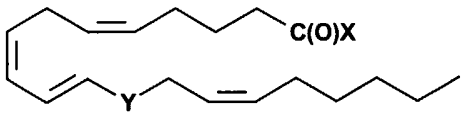
WHAT IS CLAIMED IS:

1. A method of treating dry mouth in a patient, wherein the method comprises administering to the oral cavity of the patient a composition comprising an orally acceptable carrier and a pharmaceutically effective amount of a HETE compound of formulas **I – XI**:

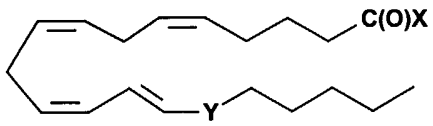
I – III:



(I)



(II); and



(III);

wherein:

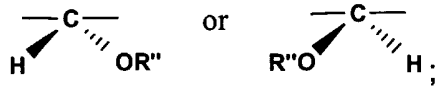
X is $O^- M^+$, OR or NHR';

M^+ is Na^+, K^+, Li^+, Cs^+, and $(A)_4N^+$; and A is independently H, alkyl, cycloalkyl, (cycloalkyl)alkyl, alkyl(cycloalkyl), aryl, arylalkyl, heteroaryl, or $(A)_4N^+$ forms a heteroaryl, heterocycloalkenyl or heterocycloalkyl ring;

R is H, substituted or unsubstituted alkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, arylalkyl, wherein the substitution is made with a moiety selected from the group consisting of: alkyl, halogen, hydroxy and functionally modified hydroxy;

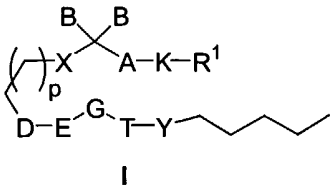
R' is H, substituted or unsubstituted alkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, arylalkyl, wherein the substitution is made with a moiety selected from the group consisting of: alkyl, halogen, hydroxy and functionally modified hydroxy; and

Y is



wherein R'' is H or C(O)R;

IV:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2-Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$, or 2,3,4,5-tetrazol-1-yl, wherein:

R is H or CO_2R forms a pharmaceutically acceptable salt or a pharmaceutically acceptable ester;

NR^2R^3 and NR^5R^6 are the same or different and comprise a free or functionally modified amino group, e.g., R^2, R^3, R^5 and R^6 are the same or different and are H, alkyl, cycloalkyl, aralkyl, aryl, OH, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 comprises a free or functionally modified hydroxy group, e.g., R^4 is H, acyl; alkyl, cycloalkyl, aralkyl, or aryl;

Hal is F, Cl, Br or I;

SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H, or $COSR^{21}$ forms a pharmaceutically acceptable salt or a pharmaceutically acceptable thioester;

K is C_2-C_8 alkyl, alkenyl, or alkynyl, or a C_3-C_8 allenyl group;

A and X are the same or different and are a direct bond, CH_2, NR^7, O, or S, with the proviso that at least one of A and X is NR^7, O, or S;

B is H, or BB together comprises a double bonded O, S, or NR^8, with the proviso that BB comprises a double bonded O, S, or NR^8 when A and X are the same or different and are NR^7, O, or S; wherein:

NR^7 and NR^8 are the same or different and comprise a functionally modified amino group, e.g., R^7 and R^8 are the same or different and are H, alkyl, cycloalkyl, aryl, aralkyl, acyl, OH, or alkoxy;

p is 0 or 1;

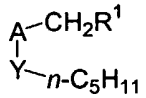
D-E, G-H are the same or different and are CH_2CH_2, CH=CH, or C≡C; and

Y is C(O) (*i.e.* a carbonyl group) or Y is

or ;

wherein R^9O constitutes a free or functionally modified hydroxy group;

V:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$, or 2,3,4,5-tetrazol-1-yl, where:

R is H or a pharmaceutically acceptable cation, or CO_2R forms a pharmaceutically acceptable ester moiety;

NR^2R^3, NR^5R^6 are the same or different and comprise a free or functionally modified amino group;

OR^4 comprises a free or functionally modified hydroxy group;

Hal is F, Cl, Br, or I;

R^{20} is H, alkyl, acyl;

R^{21} is H or a pharmaceutically acceptable cation, or $COSR^{21}$ forms a pharmaceutically acceptable thioester moiety;

A is L_1-A_1-L_2, L_1-A_2-L_2, L_3-A_2-L_4, or L_5-A_2-L_3;

A_1 is CH_2CH_2;

A_2 is

 ;

L_1 is CH_2-B-D;

B and D are the same or different and are CH_2CH_2, CH=CH, or C≡C;

L_2 is CH_2-K-CH_2CH_2;

K is CH_2CH_2, CH=CH, or C≡C;

L_3 is $CH_2CH_2CH_2$, CH_2CH=CH, CH_2C≡C, CH=$CHCH_2$, C≡CCH_2, or CH=C=CH;

L_4 is X-CH_2CH_2;

X is CH_2CH_2CH=CH, CH_2CH_2C≡C, $CH_2CH_2CH_2CH_2$, CH_2CH=$CHCH_2$, CH_2C≡CCH_2, CH=$CHCH_2CH_2$, C≡CCH_2CH_2, CH_2CH=C=CH, or CH=C=$CHCH_2$;

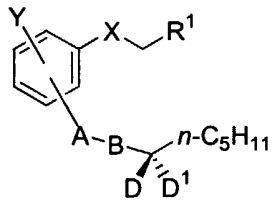
L_5 is CH_2CH_2-B-D; and

Y is C(O) (*i.e.* a carbonyl group) or Y is

or ;

wherein R^9O constitutes a free or functionally modified hydroxy group;

VI:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$ or 2,3,4,5-tetrazol-1-yl, wherein:

R is H or CO_2R forms a pharmaceutically acceptable salt or a pharmaceutically acceptable ester;

NR^2R^3 and NR^5R^6 are the same or different and comprise a free or functionally modified amino group, e.g., R^2, R^3, R^5 and R^6 are the same

or different and are H, alkyl, cycloalkyl, aralkyl, aryl, OH or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 comprises a free or functionally modified hydroxy group, e.g., R^4 is H, acyl; alkyl, cycloalkyl, aralkyl or aryl;

Hal is F, Cl, Br or I;

SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H or $COSR^{21}$ forms a pharmaceutically acceptable salt or a pharmaceutically acceptable thioester;

X is C_2-C_5 alkyl, alkynyl, or alkenyl or a C_3-C_5 allenyl group;

Y is H, free or functionally modified hydroxy group, halo, trihalomethyl, free or functionally modified amino group, free or functionally modified thiol group, $C(O)R^7$, or alkyl;

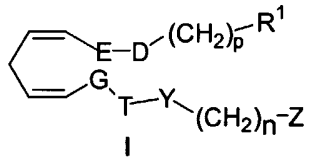
R^7 is H, OH, alkyl, alkoxy, amino, alkylamino or alkoxyamino;

A is a direct bond or C_{1-3} alkyl;

B is CH_2CH_2, *cis*- or *trans*-CH=CH, or C≡C; and

one of D and D^1 is H and the other is a free or functionally modified OH group, or DD^1 together comprises a double bonded oxygen;

VII:



wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$ or 2,3,4,5-tetrazol-1-yl, wherein:

R is H or CO_2R forms a pharmaceutically acceptable salt or a pharmaceutically acceptable ester;

NR^2R^3 and NR^5R^6 are the same or different and comprise a free or functionally modified amino group, e.g., R^2, R^3, R^5 and R^6 are the same or different and are H, alkyl, cycloalkyl, aralkyl, aryl, OH, or alkoxy, with the proviso that at most only one of R^2 and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 comprises a free or functionally modified hydroxy group, e.g., R^4 is H, acyl; alkyl, cycloalkyl, aralkyl or aryl;

Hal is F, Cl, Br or I;

SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H or $COSR^{21}$ forms a pharmaceutically acceptable salt or a pharmaceutically acceptable thioester;

E-D is $CH_2CH_2CH_2$ or *cis*-CH_2CH=CH; or E is *trans*-CH=CH and D is CH(OH) in either configuration, wherein the OH is free or functionally modified; or E is CH_2CH_2 and D is a direct bond;

p is 1 or 3 when E-D is $CH_2CH_2CH_2$ or *cis*-CH_2CH=CH, or when E is *trans*-CH=CH and D is CH(OH) in either configuration, wherein the OH is free or functionally modified; or p is 0 when E is CH_2CH_2 and D is a direct bond;

G-T is CH_2CH_2, $CH(SR^7)CH_2$ or *trans*-CH=CH;

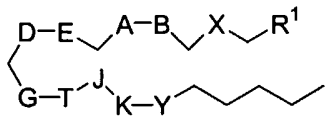
R^7 is H, alkyl, aryl, aralkyl, cycloalkyl or acyl;

Y is CH(OH) in either configuration, in which the OH is free of functionally modified, or C=O (*i.e.*, a carbonyl group);

n is 0, 2 or 4; and

Z is CH_3, CO_2R, $CONR^2R^3$ or CH_2OR^4;

VIII:



I

wherein:

R^1 is $(CH_2)_nCO_2R$, $(CH_2)_nCONR^2R^3$, $(CH_2)_nCH_2OR^4$, $(CH_2)_nCH_2NR^5R^6$, $(CH_2)_nCH_2N_3$, $(CH_2)_nCH_2Hal$, $(CH_2)_nCH_2NO_2$, $(CH_2)_nCH_2SR^{20}$, $(CH_2)_nCOSR^{21}$ or $(CH_2)_n$-2,3,4,5-tetrazol-1-yl, wherein:

R is H or CO_2R forms a pharmaceutically acceptable salt or a pharmaceutically acceptable ester;

NR^2R^3 and NR^5R^6 are the same or different and comprise a free or functionally modified amino group, e.g., R^2, R^3, R^5 and R^6 are the same or different and are H, alkyl, cycloalkyl, aralkyl, aryl, OH, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 comprises a free or functionally modified hydroxy group, e.g., R^4 is H, acyl; alkyl, cycloalkyl, aralkyl, or aryl;

Hal is F, Cl, Br or I;

SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H or $COSR^{21}$ forms a pharmaceutically acceptable salt or a pharmaceutically acceptable thioester;

n is 0 or 2;

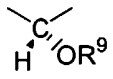
X is O, $S(O)_p$, NR^7 or CH_2, with the proviso that X cannot be CH_2 when n is 0;

p is 0, 1 or 2;

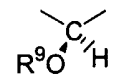
NR^7 comprises a free or functionally modified amino group, e.g., R^7 is H, alkyl, cycloalkyl, aralkyl, aryl, OH or alkoxy,

A-B, D-E, G-T and J-K are the same or different and are CH_2CH_2, CH=CH or C≡C, with the proviso that at least one of A-B, D-E, G-T and J-K must be CH=CH or C≡C; and

Y is C(O) (i.e., a carbonyl), or Y is



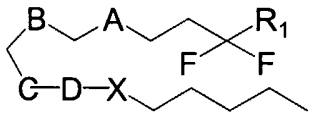
or



;

wherein R^9O constitutes a free or functionally modified hydroxy group;

IX:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$ or 2,3,4,5-tetrazol-1-yl, wherein:

R is H or CO_2R forms a pharmaceutically acceptable salt or a pharmaceutically acceptable ester;

NR^2R^3 and NR^5R^6 are the same or different and comprise a free or functionally modified amino group, e.g., R^2, R^3, R^5 and R^6 are the same or different and are H, alkyl, cycloalkyl, aralkyl, aryl, OH, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 comprises a free or functionally modified hydroxy group, e.g., R^4 is H, acyl; alkyl, cycloalkyl, aralkyl, or aryl;

Hal is F, Cl, Br or I;

SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H or $COSR^{21}$ forms a pharmaceutically acceptable salt or a pharmaceutically acceptable thioester;

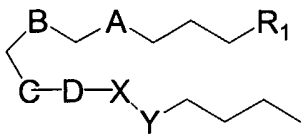
A, B, C and D are the same or different and are C_1-C_5 alkyl, alkenyl, or alkynyl or a C_3-C_5 allenyl group;

X is C(O) (*i.e.* a carbonyl group) or X is

or ;

wherein R^9O constitutes a free or functionally modified hydroxy group;

X:



I

wherein:

R^1 is $(CH_2)_nCO_2R$, $(CH_2)_nCONR^2R^3$, $(CH_2)_nCH_2OR^4$, $(CH_2)_nCH_2NR^5R^6$, $(CH_2)_nCH_2N_3$, $(CH_2)_nCH_2Hal$, $(CH_2)_nCH_2NO_2$, $(CH_2)_nCH_2SR^{20}$, $(CH_2)_nCOSR^{21}$ or $(CH_2)_n$-2,3,4,5-tetrazol-1-yl, wherein:

R is H or CO_2R forms a pharmaceutically acceptable salt or a pharmaceutically acceptable ester;

NR^2R^3 and NR^5R^6 are the same or different and comprise a free or functionally modified amino group, e.g., R^2, R^3, R^5 and R^6 are the same or different and are H, alkyl, cycloalkyl, aralkyl, aryl, OH, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 comprises a free or functionally modified hydroxy group, e.g., R^4 is H, acyl; alkyl, cycloalkyl, aralkyl, or aryl;

Hal is F, Cl, Br or I;

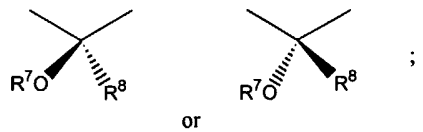
SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H or $COSR^{21}$ forms a pharmaceutically acceptable salt or a pharmaceutically acceptable thioester;

n is 0 or 2;

A, B, C and D is C_1-C_5 alkyl, alkenyl, or alkynyl or a C_3-C_5 allenyl group;

Y is



or

wherein R^8 is H or CH_3, and

X is CH_2, $CH(CH_3)$ or $C(CH_3)_2$; or

Y is CH_2, $CH(CH_3)$ or $C(CH_3)_2$, and X is

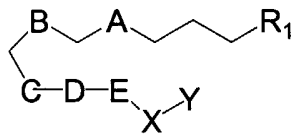
or ;

wherein R^8 is H or CH_3, with the proviso that Y cannot be CH_2 when X is

or ; and

R^7O comprises a free or functionally modified hydroxy group; and

XI:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$, or 2,3,4,5-tetrazol-1-yl, where:

R is H or a pharmaceutically acceptable cation, or CO_2R forms a pharmaceutically acceptable ester moiety;

NR^2R^3, NR^5R^6 are the same or different and comprise a free or functionally modified amino group;

OR^4 comprises a free or functionally modified hydroxy group;

Hal is F, Cl, Br, or I;

SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H or a pharmaceutically acceptable cation, or $COSR^{21}$ forms a pharmaceutically acceptable thioester moiety;

A, B, C, D are the same or different and are C_1-C_5 alkyl, C_2-C_5 alkenyl, C_{1-5} cyclopropyl, C_2-C_5 alkynyl, or a C_3-C_5 allenyl group;

E is

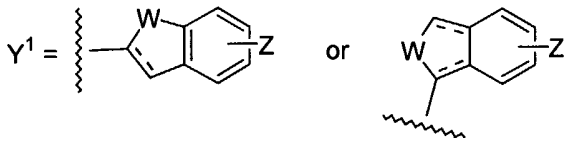
or

where OR^7 comprises a free or functionally modified hydroxy group;

X = $(CH_2)_m$ or $(CH_2)_mO$, where m = 1-6; and

Y = a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, acyl, or a free or functionally modified hydroxy, amino, or thiol group; or

X-Y = $(CH_2)_pY^1$; where p = 0-6; and



wherein:

W = CH_2, O, $S(O)_q$, NR^8, CH_2CH_2, CH=CH, CH_2O, $CH_2S(O)_q$, CH=N, or CH_2NR^8; where q = 0-2, and R^8 = H, alkyl, or acyl;

Z = H, alkyl, acyl, halo, trihalomethyl, or a free or functionally modified amino, thiol, or hydroxy group; and

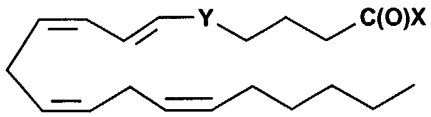
---- = single or double bond;

or X-Y = cyclohexyl.

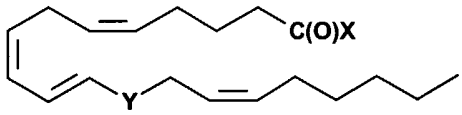
2. The method of Claim 1 wherein the HETE compound is a compound of formulas **I – III**.

3. The method of Claim 1 wherein the HETE compound is a compound of formulas **I – XI**:

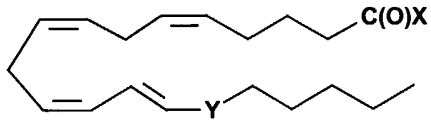
I – III:



(I)



(II); and



(III);

wherein:

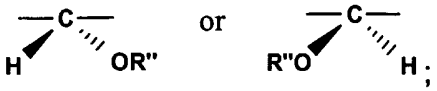
X is $O^- M^+$, OR or NHR';

M^+ is Na^+, K^+, Li^+, or Cs^+;

R is H, or substituted or unsubstituted C_{1-15} alkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, or arylalkyl, wherein the substitution is made with a moiety selected from the group consisting of: C_{1-6} alkyl, fluoro, chloro, bromo, iodo, OH, $OCH_2C(O)CH_3$,$OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, and $OC(O)C_2H_5$;

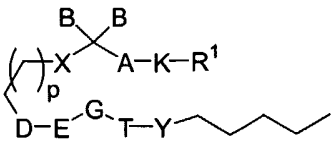
R' is H, or substituted or unsubstituted C_{1-15} alkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, or arylalkyl, wherein the substitution is made with a moiety selected from the group consisting of: C_{1-6} alkyl, fluoro, chloro, bromo, iodo, OH, $OCH_2C(O)CH_3$,$OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, and $OC(O)C_2H_5$; and

Y is



wherein R'' is H or C(O)R;

IV:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2-Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$, or 2,3,4,5-tetrazol-1-yl, wherein:

R is H, Na^+, K^+, Li^+, Cs^+, $(A)_4N^+$, or C_{1-15} alkyl, cycloalkyl, arylalkyl, aryl or alkoxy;
A is independently H or C_{1-15} alkyl, cycloalkyl, (cycloalkyl)alkyl, alkyl(cycloalkyl), aryl, arylalkyl, heteroaryl, or $(A)_4N^+$ forms a heteroaryl, heterocycloalkenyl or heterocycloalkyl ring;

R^2, R^3, R^5 and R^6 are the same or different and are H, OH, or C_{1-15} alkyl, cycloalkyl, arylalkyl, aryl, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 is OH, $OCH_2C(O)CH_3$, $OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$;

Hal is F, Cl, Br or I;

SR^{20} is SH, $SC(O)CH_3$, SCH_3, SC_2H_5, $SCH_2C(O)C_2H_5$, and $SCH_2C(O)CH_3$;

R^{21} is H or C_{1-15} alkyl or aryl;

K is C_2-C_8 alkyl, alkenyl, or alkynyl, or a C_3-C_8 allenyl group;

A and X are the same or different and are a direct bond, CH_2, NR^7, O, or S, with the proviso that at least one of A and X is NR^7, O, or S;

B is H, or BB together comprises a double bonded O, S, or NR^8, with the proviso that BB comprises a double bonded O, S, or NR^8 when A and X are the same or different and are NR^7, O, or S; wherein:

R^7 and R^8 are the same or different and are H, OH, or C_{1-15} alkyl, cycloalkyl, aryl, aralkyl, acyl, or alkoxy;

p is 0 or 1;

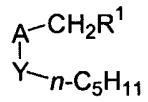
D-E, G-H are the same or different and are CH_2CH_2, CH=CH, or C≡C; and

Y is C(O) or

or ;

wherein OR^9 is OH, $OCH_2C(O)CH_3$,$OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$;

V:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$, or 2,3,4,5-tetrazol-1-yl, where:

R is H, Na^+, K^+, Li^+, Cs^+, $(A)_4N^+$, or $C_{1\text{-}15}$ alkyl, cycloalkyl, arylalkyl, aryl or alkoxy;

A is independently H or $C_{1\text{-}15}$ alkyl, cycloalkyl, (cycloalkyl)alkyl, alkyl(cycloalkyl), aryl, arylalkyl, heteroaryl, or $(A)_4N^+$ forms a heteroaryl, heterocycloalkenyl or heterocycloalkyl ring;

R^2, R^3, R^5 and R^6 are the same or different and are H, OH, or $C_{1\text{-}15}$ alkyl, cycloalkyl, arylalkyl, aryl, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 is OH, $OCH_2C(O)CH_3$, $OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$;

Hal is F, Cl, Br, or I;

R^{20} is H or $C_{1\text{-}15}$ alkyl or acyl;

R^{21} is H or $C_{1\text{-}15}$ alkyl or aryl;

A is L_1-A_1-L_2, L_1-A_2-L_2, L_3-A_2-L_4, or L_5-A_2-L_3;

A_1 is CH_2CH_2;

A_2 is

 ;

L_1 is CH_2-B-D;

B and D are the same or different and are CH_2CH_2, CH=CH, or C≡C;

L_2 is CH_2-K-CH_2CH_2;

K is CH_2CH_2, CH=CH, or C≡C;

L_3 is $CH_2CH_2CH_2$, CH_2CH=CH, CH_2C≡C, CH=$CHCH_2$, C≡CCH_2, or CH=C=CH;

L_4 is X-CH_2CH_2;

X is CH_2CH_2CH=CH, CH_2CH_2C≡C, $CH_2CH_2CH_2CH_2$, CH_2CH=$CHCH_2$, CH_2C≡CCH_2, CH=$CHCH_2CH_2$, C≡CCH_2CH_2, CH_2CH=C=CH, or CH=C=$CHCH_2$;

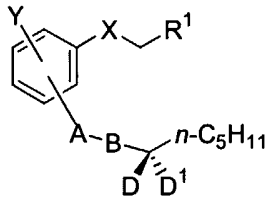
L_5 is CH_2CH_2-B-D; and

Y is C(O) or

or ;

wherein OR^9 is OH, $OCH_2C(O)CH_3$,$OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$;

VI:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$ or 2,3,4,5-tetrazol-1-yl, wherein:

R is H, Na^+, K^+, Li^+, Cs^+, $(A)_4N^+$, or $C_{1\text{-}15}$ alkyl, cycloalkyl, arylalkyl, aryl or alkoxy;

A is independently H or $C_{1\text{-}15}$ alkyl, cycloalkyl, (cycloalkyl)alkyl, alkyl(cycloalkyl), aryl, arylalkyl, heteroaryl, or $(A)_4N^+$ forms a heteroaryl, heterocycloalkenyl or heterocycloalkyl ring;

R^2, R^3, R^5 and R^6 are the same or different and are H, OH, or C_{1-15} alkyl, cycloalkyl, arylalkyl, aryl, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 is OH, $OCH_2C(O)CH_3$, $OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$;

Hal is F, Cl, Br or I;

SR^{20} is SH, $SC(O)CH_3$, SCH_3, SC_2H_5, $SCH_2C(O)C_2H_5$, and $SCH_2C(O)CH_3$;

R^{21} is H or C_{1-15} alkyl or aryl;

X is C_2-C_5 alkyl, alkynyl, or alkenyl or a C_3-C_5 allenyl group;

Y is H, $OCH_2C(O)CH_3$, $OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$, Hal, $C(Hal)_3$, NH_2, $NHCH_3$, NHC_2H_5, $N(CH_3)_2$, $NHC(O)CH_3$, NHOH, $NH(OCH_3)$, SH, $SC(O)CH_3$, SCH_3, SC_2H_5, $SCH_2C(O)C_2H_5$, $SCH_2C(O)CH_3$, $C(O)R^7$, or C_{1-15} alkyl;

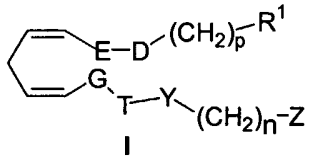
R^7 is H, OH, or C_{1-15} alkyl, alkoxy, amino, alkylamino or alkoxyamino;

A is a direct bond or C_{1-3} alkyl;

B is CH_2CH_2, *cis*- or *trans*-CH=CH, or C≡C; and

one of D and D^1 is H and the other is OH, $OCH_2C(O)CH_3$, $OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$, or DD^1 together comprises a double bonded oxygen;

VII:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$ or 2,3,4,5-tetrazol-1-yl, wherein:

R is H, Na^+, K^+, Li^+, Cs^+, $(A)_4N^+$, or C_{1-15} alkyl, cycloalkyl, arylalkyl, aryl or alkoxy;

A is independently H or C_{1-15} alkyl, cycloalkyl, (cycloalkyl)alkyl, alkyl(cycloalkyl), aryl, arylalkyl, heteroaryl, or $(A)_4N^+$ forms a heteroaryl, heterocycloalkenyl or heterocycloalkyl ring;

R^2, R^3, R^5 and R^6 are the same or different and are H, OH, or C_{1-15} alkyl, cycloalkyl, arylalkyl, aryl, or alkoxy, with the proviso that at most only one of R^2 and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 is OH, $OCH_2C(O)CH_3$, $OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$;

Hal is F, Cl, Br or I;

SR^{20} is SH, $SC(O)CH_3$, SCH_3, SC_2H_5, $SCH_2C(O)C_2H_5$, and $SCH_2C(O)CH_3$;

R^{21} is H or C_{1-15} alkyl or aryl;

E-D is $CH_2CH_2CH_2$ or *cis*-$CH_2CH{=}CH$; or E is *trans*-CH=CH and D is CH(X) in either configuration, wherein X is OH, $OCH_2C(O)CH_3$, $OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$; or E is CH_2CH_2 and D is a direct bond;

p is 1 or 3 when E-D is $CH_2CH_2CH_2$ or *cis*-$CH_2CH{=}CH$, or when E is *trans*-CH=CH and D is CH(X) in either configuration; or p is 0 when E is CH_2CH_2 and D is a direct bond;

G-T is CH_2CH_2, $CH(SR^7)CH_2$ or *trans*-CH=CH;

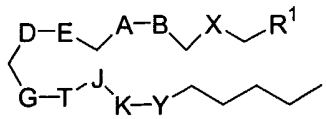
R^7 is H, or C_{1-15} alkyl, aryl, aralkyl, cycloalkyl or acyl;

Y is CH(X) in either configuration, or C(O);

n is 0, 2 or 4; and

Z is CH_3, CO_2R, $CONR^2R^3$ or CH_2OR^4;

VIII:



I

wherein:

R^1 is $(CH_2)_nCO_2R$, $(CH_2)_nCONR^2R^3$, $(CH_2)_nCH_2OR^4$, $(CH_2)_nCH_2NR^5R^6$, $(CH_2)_nCH_2N_3$, $(CH_2)_nCH_2Hal$, $(CH_2)_nCH_2NO_2$, $(CH_2)_nCH_2SR^{20}$, $(CH_2)_nCOSR^{21}$ or $(CH_2)_n$-2,3,4,5-tetrazol-1-yl, wherein:

R is H, Na^+, K^+, Li^+, Cs^+, $(A)_4N^+$, or $C_{1\text{-}15}$ alkyl, cycloalkyl, arylalkyl, aryl or alkoxy;

A is independently H or $C_{1\text{-}15}$ alkyl, cycloalkyl, (cycloalkyl)alkyl, alkyl(cycloalkyl), aryl, arylalkyl, heteroaryl, or $(A)_4N^+$ forms a heteroaryl, heterocycloalkenyl or heterocycloalkyl ring;

R^2, R^3, R^5 and R^6 are the same or different and are H, OH, or $C_{1\text{-}15}$ alkyl, cycloalkyl, arylalkyl, aryl, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 is OH, $OCH_2C(O)CH_3$, $OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$;

Hal is F, Cl, Br or I;

SR^{20} is SH, $SC(O)CH_3$, SCH_3, SC_2H_5, $SCH_2C(O)C_2H_5$, and $SCH_2C(O)CH_3$;

R^{21} is H or $C_{1\text{-}15}$ alkyl or aryl;

n is 0 or 2;

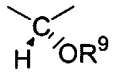
X is O, $S(O)_p$, NR^7 or CH_2, with the proviso that X cannot be CH_2 when n is 0;

p is 0, 1 or 2;

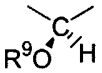
R^7 is H, OH or $C_{1\text{-}15}$ alkyl, cycloalkyl, aralkyl, aryl, or alkoxy,

A-B, D-E, G-T and J-K are the same or different and are CH_2CH_2, CH=CH or C≡C, with the proviso that at least one of A-B, D-E, G-T and J-K must be CH=CH or C≡C; and

Y is C(O), or



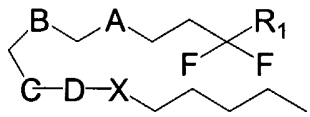
or



;

wherein OR^9 is OH, $OCH_2C(O)CH_3$,$OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$;

IX:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$ or 2,3,4,5-tetrazol-1-yl, wherein:

R is H, Na^+, K^+, Li^+, Cs^+, $(A)_4N^+$, or $C_{1\text{-}15}$ alkyl, cycloalkyl, arylalkyl, aryl or alkoxy;

A is independently H or $C_{1\text{-}15}$ alkyl, cycloalkyl, (cycloalkyl)alkyl, alkyl(cycloalkyl), aryl, arylalkyl, heteroaryl, or $(A)_4N^+$ forms a heteroaryl, heterocycloalkenyl or heterocycloalkyl ring;

R^2, R^3, R^5 and R^6 are the same or different and are H, OH, or $C_{1\text{-}15}$ alkyl, cycloalkyl, arylalkyl, aryl, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 is OH, $OCH_2C(O)CH_3$, $OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$;

Hal is F, Cl, Br or I;

SR^{20} is SH, $SC(O)CH_3$, SCH_3, SC_2H_5, $SCH_2C(O)C_2H_5$, and $SCH_2C(O)CH_3$;

R^{21} is H or $C_{1\text{-}15}$ alkyl or aryl;

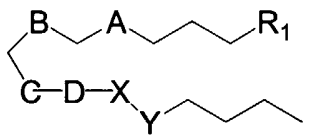
A, B, C and D are the same or different and are C_1-C_5 alkyl, alkenyl, or alkynyl or a C_3-C_5 allenyl group;

X is C(O) or

or ;

wherein OR^9 is OH, $OCH_2C(O)CH_3$,$OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$;

X:



I

wherein:

R^1 is $(CH_2)_nCO_2R$, $(CH_2)_nCONR^2R^3$, $(CH_2)_nCH_2OR^4$, $(CH_2)_nCH_2NR^5R^6$, $(CH_2)_nCH_2N_3$, $(CH_2)_nCH_2Hal$, $(CH_2)_nCH_2NO_2$, $(CH_2)_nCH_2SR^{20}$, $(CH_2)_nCOSR^{21}$ or $(CH_2)_n$-2,3,4,5-tetrazol-1-yl, wherein:

R is H, Na^+, K^+, Li^+, Cs^+, $(A)_4N^+$, or $C_{1\text{-}15}$ alkyl, cycloalkyl, arylalkyl, aryl or alkoxy;

A is independently H or $C_{1\text{-}15}$ alkyl, cycloalkyl, (cycloalkyl)alkyl, alkyl(cycloalkyl), aryl, arylalkyl, heteroaryl, or $(A)_4N^+$ forms a heteroaryl, heterocycloalkenyl or heterocycloalkyl ring;

R^2, R^3, R^5 and R^6 are the same or different and are H, OH, or $C_{1\text{-}15}$ alkyl, cycloalkyl, arylalkyl, aryl, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 is OH, $OCH_2C(O)CH_3$, $OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$;

Hal is F, Cl, Br or I;

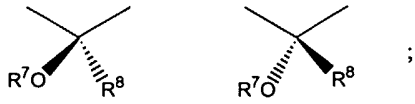
SR^{20} is SH, $SC(O)CH_3$, SCH_3, SC_2H_5, $SCH_2C(O)C_2H_5$, and $SCH_2C(O)CH_3$;

R^{21} is H or $C_{1\text{-}15}$ alkyl or aryl;

n is 0 or 2;

A, B, C and D is C_1-C_5 alkyl, alkenyl, or alkynyl or a C_3-C_5 allenyl group;

Y is

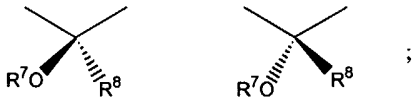


or

wherein R^8 is H or CH_3, and

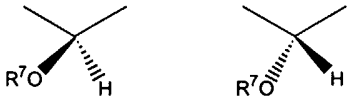
X is CH_2, $CH(CH_3)$ or $C(CH_3)_2$; or

Y is CH_2, $CH(CH_3)$ or $C(CH_3)_2$, and X is



or

wherein R^8 is H or CH_3, with the proviso that Y cannot be CH_2 when X is

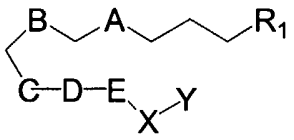


or

; and

R^7O is OH, $OCH_2C(O)CH_3$,$OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$; and

XI:



I

wherein:

R^1 is CO_2R, $CONR^2R^3$, CH_2OR^4, $CH_2NR^5R^6$, CH_2N_3, CH_2Hal, CH_2NO_2, CH_2SR^{20}, $COSR^{21}$, or 2,3,4,5-tetrazol-1-yl, where:

R is H, Na^+, K^+, Li^+, Cs^+, $(A)_4N^+$, or C_{1-15} alkyl, cycloalkyl, arylalkyl, aryl or alkoxy;

A is independently H or C_{1-15} alkyl, cycloalkyl, (cycloalkyl)alkyl, alkyl(cycloalkyl), aryl, arylalkyl, heteroaryl, or $(A)_4N^+$ forms a heteroaryl, heterocycloalkenyl or heterocycloalkyl ring;

R^2, R^3, R^5 and R^6 are the same or different and are H, OH, or C_{1-15} alkyl, cycloalkyl, arylalkyl, aryl, or alkoxy, with the proviso that at most only one of $R^2$and R^3 are OH or alkoxy and at most only one of R^5 and R^6 are OH or alkoxy;

OR^4 is OH, $OCH_2C(O)CH_3$, $OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$;

Hal is F, Cl, Br or I;

SR^{20} is SH, $SC(O)CH_3$, SCH_3, SC_2H_5, $SCH_2C(O)C_2H_5$, and $SCH_2C(O)CH_3$;

R^{21} is H or C_{1-15} alkyl or aryl;

A, B, C, D are the same or different and are C_1-C_5 alkyl, C_2-C_5 alkenyl, C_{1-5} cyclopropyl, C_2-C_5 alkynyl, or a C_3-C_5 allenyl group;

E is

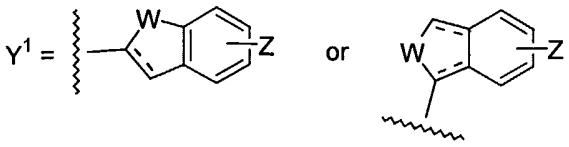
or ;

where OR^7 is OH, $OCH_2C(O)CH_3$,$OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, or $OC(O)C_2H_5$;

X = $(CH_2)_m$ or $(CH_2)_mO$, where m = 1-6; and

Y = a phenyl ring optionally substituted with C_{1-6} alkyl or acyl, Hal, $C(Hal)_3$, OH, $OCH_2C(O)CH_3$,$OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, $OC(O)C_2H_5$, NH_2, $NHCH_3$, NHC_2H_5, $N(CH_3)_2$, $NHC(O)CH_3$, NHOH, $NH(OCH_3)$., SH, $SC(O)CH_3$, SCH_3, SC_2H_5, $SCH_2C(O)C_2H_5$, or $SCH_2C(O)CH_3$; and

X-Y = $(CH_2)_pY^1$; where p = 0-6; and



wherein:

W = CH_2, O, $S(O)_q$, NR^8, CH_2CH_2, CH=CH, CH_2O, $CH_2S(O)_q$, CH=N, or CH_2NR^8; where q = 0-2, and R^8 = H, or C_{1-15} alkyl or acyl;

Z = H, C_{1-15} alkyl or acyl, Hal, $C(Hal)_3$, OH, $OCH_2C(O)CH_3$,$OCH_2C(O)C_2H_5$, OCH_3, OCH_2CH_3, $OC(O)CH_3$, $OC(O)C_2H_5$, NH_2, $NHCH_3$, NHC_2H_5, $N(CH_3)_2$, $NHC(O)CH_3$, NHOH, $NH(OCH_3)$., SH, $SC(O)CH_3$, SCH_3, SC_2H_5, $SCH_2C(O)C_2H_5$, or $SCH_2C(O)CH_3$; and

---- = single or double bond;

or X-Y = cyclohexyl.

4. The method of Claim 1 wherein the HETE compound is present in the composition in a concentration range of 0.000001 to 10 %w/v.

5. The method of Claim 4 wherein the HETE compound is present in the composition in a concentration range of 0.00001-0.01% w/v.

6. The method of Claim 1 wherein the orally acceptable carrier is selected from the group consisting of a mouth rinse; a toothpaste; a syrup, a chewing gum; and a dissolving tablet.

WO 03/105823 RNATIONAL SEARCH REPORT

International Application No
PCT/US PCT/US03/10817

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/202 A61K31/131 A61K31/16 A61K31/22 A61K31/41
A61K31/404 A61K31/381 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 05388 A (UENO SEIYAKU OYO KENKYUJO KK) 25 January 2001 (2001-01-25) page 1, line 6-25 page 9, line 8-19 page 10, line 2-23 page 27, line 18 -page 28, line 1,10-16 page 29, line 22-25 page 31, line 8-12	1-6
Y	WO 01 34549 A (ALCON UNIVERSAL LTD ;SCHNEIDER L WAYNE (US); BHAGAT HARESH G (US);) 17 May 2001 (2001-05-17) page 1, line 5-7 page 4, line 9-12 page 6, line 5-7 page 8, line 10 -page 9, line 10	1-6

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 August 2003	26/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Houyvet, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/10817

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/10817

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 34129 A (ALCON UNIVERSAL LTD ;KLIMKO PETER G (US); CONROW RAYMOND E (US)) 17 May 2001 (2001-05-17) page 1, line 5-7 page 4, line 8-11 page 5, line 3-14 page 6, line 4-7,14-20 page 7, line 1 -page 8, line 19	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/10817

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0105388 A	25-01-2001	AU 5853300 A	05-02-2001
		BR 0012387 A	26-03-2002
		CA 2377661 A1	25-01-2001
		CN 1399548 T	26-02-2003
		CZ 20020133 A3	12-06-2002
		EP 1223925 A2	24-07-2002
		HU 0202400 A2	28-11-2002
		WO 0105388 A2	25-01-2001
		JP 2003504397 T	04-02-2003
		NO 20020133 A	13-03-2002
		TR 200200065 T2	21-10-2002
		US 6566398 B1	20-05-2003
WO 0134549 A	17-05-2001	AU 1101401 A	06-06-2001
		BR 0015436 A	16-07-2002
		CA 2388044 A1	17-05-2001
		CN 1387503 T	25-12-2002
		EP 1228028 A1	07-08-2002
		JP 2003513949 T	15-04-2003
		TR 200201250 T2	23-09-2002
		WO 0134549 A1	17-05-2001
		US 6429227 B1	06-08-2002
		AU 1340801 A	06-06-2001
		BR 0015416 A	16-07-2002
		CN 1387505 T	25-12-2002
		EP 1228032 A1	07-08-2002
		JP 2003513951 T	15-04-2003
		TR 200201246 T2	23-09-2002
		WO 0134554 A1	17-05-2001
		US 6353022 B1	05-03-2002
WO 0134129 A	17-05-2001	AU 8031500 A	06-06-2001
		BR 0015423 A	09-07-2002
		CA 2386623 A1	17-05-2001
		CN 1382046 T	27-11-2002
		EP 1227809 A2	07-08-2002
		JP 2003513910 T	15-04-2003
		TR 200201249 T2	23-09-2002
		WO 0134129 A2	17-05-2001
		US 6331566 B1	18-12-2001
		US 2002002196 A1	03-01-2002
		US 2001051648 A1	13-12-2001